



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/613,736

07/03/2003

Arthur M. Krieg

C1037.70044US00

4723

7590 01/11/2010
Maria A. Trevisan
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, MA 02210

EXAMINER

ARCHIE, NINA

ART UNIT

PAPER NUMBER

1645

MAIL DATE

DELIVERY MODE

01/11/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/613,736	Applicant(s) KRIEG, ARTHUR M.	
	Examiner Nina A. Archie	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 9/28/2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) 14, 15, 45, 46, 50-53, 57, 63, 70-80, 84, 88, 95, 97 and 100 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1-13, 20, 22, 27-32, 43 and 99 is/are allowed.
- 6) ☒ Claim(s) 16, 18 and 19 is/are rejected.
- 7) ☒ Claim(s) 17 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>9/25/2009</u> . | 6) <input type="checkbox"/> Other: _____ |

Continuation of Disposition of Claims: Claims pending in the application are 1-20,22,27-32,43,45,46,50-53,57,63,70-73,76-80,84,88,95,97,99 and 100.

DETAILED ACTION

1. This Office is responsive to Applicant's amendment and response filed 9-28-09. Claims 1-20, 22, 27-32, 43, 45-46, 50-53, 57, 63, 70-73, 76-80, 84, 88, 95, 97, and 99-100 are pending. Claims 1-13, 16-20, 22, 27-32, 43, and 99 are under examination. Claims 14-15, 45-46, 50-53, 57, 63, 70-80, 84, 88, 95, 97, and 100 are withdrawn. Claims 99-100 are new. Claims 1 and 22 are amended.

Election/Restriction

2. Newly submitted claim 100 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Applicant has an elected invention on 11/13/2007 and the instant application has been examined. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 100 has been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Information Disclosure Statement

3. The information disclosure statement filed on 9/25/2009 has been considered. An initialed copy is enclosed.

Rejections Withdrawn

4. In view of the Applicant's amendment and remark following rejections are withdrawn.
a) Rejection of claim 17 under 35 U.S.C. 112 first paragraph is withdrawn in light of applicant's argument.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

5. The rejection of claims 16 and 18-19 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement are maintained for the reasons set forth in the previous office action. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant arguments:

Applicants arguments filed in response to the 35 U.S.C. 112 first paragraph, September 28, 2009 is carefully considered, but not found to be persuasive for the reasons below.

A) Applicants argue the specification discloses multiple species of backbone modifications that can be applied to an immunostimulatory nucleic acid sequence comprising SEQ ID NO: 1. Applicants state the specification describes species of the claimed genus of backbone modifications and describes distinguishing identifying characteristics of such modifications; see for example, page 16 lines 1-25 which discloses backbone modifications such as modified internucleoside bridges and dephospho bridges; see page 19 lines 5-9 which discloses specific backbone modifications including phosphorothioate linkages, phosphodiester modified nucleic acids, combinations of phosphodiester and phosphorothioate nucleic acid, methylphosphonate, methylphosphorothioate, phosphorodithioate, p-ethoxy, and combinations thereof; page 20, lines 15-26 and page 21 lines 3-9 which discloses chimeric molecules.

B) Applicants submits the reference Krieg et al. Antisense and Nucleic Acid Drug Development (1996) 6:133-139 depicted in Figure 1, that all of the immunostimulatory nucleic acids showed a dose-dependent immunostimulatory capacity (See Figs. 1-3) and the only sequences that exhibited no dose-dependent increase in immunostimulatory activity were the negative controls that lacked CpG dinucleotides and in other words, as dose increased, all immunostimulatory nucleic acids, but not the negative control nucleic acids, showed immunostimulatory activity, albeit to different levels. Applicants state that optimization of dosages can be achieved through routine experimentation using assays such as those presented in

Art Unit: 1645

Krieg et al. and Yu et al. Applicants argue the presence of a CpG motif can affect the degree of immunostimulatory capacity of a nucleic acid such as an example from Hartmann et al. Immunology (2000) 164:1617-1624, page 1621, left column, which discloses an optimal 8 nucleotide motif (TCGTCGTT) and an optimal 6 nucleotide motif (GTCGTT) for stimulation of human B cells. Applicants state a sequence that contains the optimal 8 nucleotide motif on the 5' end and also contains an optimal 6 nucleotide motif was more immunostimulatory than a sequence containing a CpG motif that is optimal for activating mouse cells (GACGTT). Applicants argue that the sequence disclosed in the Yu et al. reference, cited by the Examiner, contains only one CpG motif, and this CpG motif is in a sequence context that is optimal for activating mouse cells and by contrast, the claimed sequence, SEQ ID NO: 1, contains four CpG motifs including the 8 nucleotide motif that is optimal for human cells, on the 5' end, and the 6 nucleotide motif that is also optimal for human cells. Hartmann et al. teaches that nucleic acids having such motifs are more immunostimulatory than nucleic acids containing an optimal motif for mouse cells, as does the sequence of Yu et al. Applicants argue that the teachings of Yu et al. are not clearly transferable to nucleic acids comprising SEQ ID NO: 1 which, unlike the sequence of Yu et al., comprises four CpG dinucleotides, one of which is a reported optimal 8 nucleotide motif for human cells and another of which is a reported optimal 6 nucleotide motif for human cells. Applicants state that one of skill in the art would appreciate that even if a backbone modification reduced the immunostimulatory capacity of a nucleic acid, if the nucleic acid is highly immunostimulatory to begin with, the reduction may not be as significant as in a weakly immunostimulatory nucleic acid. Applicants state that in a nucleic acid that has multiple immunostimulatory motifs, such as multiple CpG motifs, a backbone modification may reduce the immunostimulatory capacity of one of the motifs without impacting the immunostimulatory activity of the other motifs.

Examiner's Response to Applicant arguments:

In response to applicant does statement in (A) as set forth supra, Applicants response stating that the specification discloses multiple species of backbone modifications that can be applied to an immunostimulatory nucleic acid sequence comprise SEQ ID NO: 1 is unpersuasive for the reasons as set forth supra. To begin with, the independent claim is drawn to a composition comprising an immunostimulatory nucleic acid comprising the nucleotide sequence of SEQ ID

Art Unit: 1645

NO: 1, wherein the immunostimulatory nucleic acid has a nucleotide backbone which includes at least one backbone modification, however, the specification is only limited to the immunostimulatory nucleic acid comprising SEQ ID NO: 1 also known as in the art as ODN 10105 (see pgs. 12 and 87). Also the instant claims encompass an immunostimulatory nucleic acid that includes both those that are methylated and unmethylated. The specification does not provide adequate description of the claimed genus of nucleotide backbone modifications in an immunostimulatory nucleic acid. Moreover, Applicant has not demonstrated which nucleotide backbone modifications in an immunostimulatory nucleic acid possess the abilities of the claimed immunostimulatory nucleic acid of SEQ ID NO: 1. Consequently, the number of species disclosed by the specification is not representative of the genus of nucleotide backbone modifications in an immunostimulatory nucleic acid encompassed by the claimed genus. Applicant is reminded that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Therefore the written description rejection is maintained.

In response to applicant's statement in (B) as set forth supra, in regards to the reference of Krieg et al. *Antisense and Nucleic Acid Drug Development* (1996) 6:133-139 cited by Applicants to show that all of the immunostimulatory nucleic acids showed a dose-dependent immunostimulatory capacity (See Figs. 1-3) and the only sequences that exhibited no dose-dependent increase in immunostimulatory activity were the negative controls that lacked CpG dinucleotides does not indicate the genus and thus is unpersuasive. The claims are specifically drawn to a composition comprising an immunostimulatory nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1, wherein the immunostimulatory nucleic acid has a nucleotide backbone which includes at least one backbone modification and do not indicate the genus of nucleotide backbone modifications in an immunostimulatory nucleic acid. Moreover, in regards to Applicants response, that the art discloses a sequence that contains the optimal 8 nucleotide motif on the 5' end and also contains an optimal 6 nucleotide motif was more immunostimulatory than a sequence containing a CpG motif that is optimal for activating mouse cells (GACGTT) and the art disclosed by Hartman et al is not relevant to the claims. Moreover, in regards to Applicants response, that one of skill in the art would appreciate that even if a

Art Unit: 1645

backbone modification reduced the immunostimulatory capacity of a nucleic acid, if the nucleic acid is highly immunostimulatory to begin with, the reduction may not be as significant as in a weakly immunostimulatory nucleic acid is not relevant to the instant claims. For the reasons that Point 1: the claims are directed to a composition comprising an immunostimulatory nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1, wherein the immunostimulatory nucleic acid has a nucleotide backbone which includes at least one backbone modification; Point 2: as indicated by Yu et al, the art has not determined whether any immunostimulatory nucleic acid with any modified backbone is able to possess the abilities of the claimed immunostimulatory nucleic acid. Furthermore, Yu et al is cited to reveal the effects of oligonucleotides and structural changes that potentiate or suppress immunostimulatory activities of CpG oligos and also reveal oligonucleotides with no non-ionic linkage showed the ability to induce cell proliferation, however replacing a negatively charged phosphorothioate internucleoside linkage with a non-ionic methylphosphonate linkage resulted in the loss of lymphocyte proliferative activity which show that the state of the art is unpredictable to the claimed invention and therefore the claimed invention is not properly disclosed.

As outlined previously, the claims are drawn to a composition, wherein the immunostimulatory nucleic acid has a nucleotide backbone which includes at least one backbone modification (claim 16), wherein the nucleotide backbone is chimeric (claim 18), wherein the nucleotide backbone is entirely modified (claim 19).

To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession of the claimed invention. To adequately describe the genus of nucleotide backbone modifications in an immunostimulatory nucleic acid.

The specification discloses immunostimulatory nucleic acid comprising SEQ ID NO: 1 also known as in the art as ODN 10105 (see pgs. 12 and 87). The specification discloses nucleotide backbone modifications (see pg. 4 and 19). The specification discloses various

Art Unit: 1645

chemical modifications and substitutions (see pg. 16 lines 1-5). The specification does not provide adequate description of the claimed genus of nucleotide backbone modifications in an immunostimulatory nucleic acid.

Applicant has not demonstrated which nucleotide backbone modifications in an immunostimulatory nucleic acid possess the abilities of the claimed immunostimulatory nucleic acid of SEQ ID NO: 1. The limited number of nucleotide backbone modifications in an immunostimulatory nucleic acid disclosed is not deemed to be representative of the genus encompassed by the instant claims. The specification, does not disclose distinguishing and identifying features of a representative number of members of the genus of nucleotide backbone modifications in an immunostimulatory nucleic acid, to which the claims are drawn, such as a correlation between the structure of the nucleotide backbone modifications in an immunostimulatory nucleic acid and its recited function immunostimulatory activity, so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of nucleotide backbone modifications in an immunostimulatory nucleic acid.

Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of nucleotide backbone modifications in an immunostimulatory nucleic acid aforementioned above to which the claims are based.

MPEP § 2163.02 states, “[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ”. The courts have decided:

The purpose of the “written description” requirement is broader than to merely explain how to “make and use”; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the “written description” inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical*

Co. Ltd., 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (*Id.* at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Yu et al (Yu et al 2001 *Biorganic & Medicinal Chemistry* Vol. 9 Issue 11 pgs. 2803-2808), whom study the effects of oligonucleotides and structural changes that potentiate or suppress immunostimulatory activities of CpG oligos. Yu et al teach oligonucleotides with no non-ionic linkage showed the ability to induce cell proliferation, however replacing a negatively charged phosphorothioate internucleoside linkage with a non-ionic methylphosphonate linkage resulted in the loss of lymphocyte proliferative activity (see "Effect of non-ionic internucleoside methylphosphonate linkage in the 5'-flanking sequence" pg. 2804 column 2). Furthermore Yu et al teaches that the non-ionic phosphate linkages may enhance suppress, or maintain immunostimulatory activity compared with an unmodified CpG

Art Unit: 1645

oligo, depending on the position of the substitution (see pg. 2806 column 1). Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of nucleotide backbone modifications in an immunostimulatory nucleic acid, the skilled artisan could not immediately recognize or distinguish members of the claimed genus aforementioned above. Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of the genus of nucleotide backbone modifications in an immunostimulatory nucleic acid is not deemed representative of the genus of the recited composition to which the claims refer and therefore the claimed invention is not properly disclosed.

Enablement

6. The rejection of claims 16 and 18-19 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement are maintained for the reasons set forth in the previous office action. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant arguments:

A) Level of ordinary skill in the art. Applicants state the person of ordinary skill in the art would be familiar with synthesis and optimization of immunostimulatory nucleic acids including the incorporation of backbone modifications, as shown by the cited art.

B) State of the art and unpredictability in the art. Applicants state that even the nucleic acids that exhibited reduced immunostimulatory capacity in Yu et al., such as sequences 2, 3 and 4 in Table 1, were not rendered inert by the backbone modification, but rather showed a dose-dependent stimulation of IL-12, that was similar to the other sequences in Table 1 just at a lower level. Applicants' state that in fact, Yu et al. states on page 2804, right column, that "[a]ll the oligos showed a concentration-dependent lymphocyte proliferation." Applicants state this reference reveals a predictable trend of dose-dependent immunostimulatory capacity of nucleic acids and based on this reference, one of ordinary skill in the art would have predicted that a backbone modification would not render inert an immunostimulatory nucleic acid. Applicants state that one of ordinary skill in the art would have predicted that a reduction in immunostimulatory capacity, due to such modification, could be alleviated through

Art Unit: 1645

administration of a higher dose of the nucleic acid. Applicants state that Krieg et al. did not find backbone modifications that rendered any of the nucleic acids tested inert and immunostimulatory nucleic acids showed a dose-dependent immunostimulatory capacity, regardless of their backbone modifications (see Figs. 1-3) and the only nucleic acids which did not exhibit such dose-dependent increase in immunostimulatory capacity were the negative control nucleic acids that lacked CpG dinucleotides. Applicants state that Hartmann et al, submitted herewith, discloses on page 1621, left column an optimal 8 nucleotide motif (TCGTCGTT) and an optimal 6 nucleotide motif (GTCGTT) for stimulation of human B cells. Applicants state that the authors disclose that a sequence that contains the human optimal 8 nucleotide motif on the 5' end and also contains an optimal 6 nucleotide motif was more immunostimulatory than a sequence containing a CpG motif that is optimal for activating mouse cells (GACGTT). Applicants state that the claimed sequence, SEQ ID NO: 1, contains four CpG motifs including the 8 nucleotide motif that is optimal for human cells, on the 5' end, and the 6 nucleotide motif that is also optimal for human cells. Applicants state that one of skill in the art would appreciate that even if a backbone modification reduced the immunostimulatory capacity of a nucleic acid, if the nucleic acid is highly immunostimulatory to begin with, the reduction may not be as significant as in a weakly immunostimulatory nucleic acid. Applicants state that in a nucleic acid that has multiple immunostimulatory motifs, such as multiple CpG motifs, a backbone modification may reduce the immunostimulatory capacity of one of the motifs without impacting the immunostimulatory activity of the other motifs. Applicants state that the specification also provides multiple other references that indicate the state of the art regarding backbone modifications in an immunostimulatory nucleic acid as of the filing date of the instant application, for example, page 19 lines 9-14 of the specification incorporate by reference disclosure related to specific backbone modifications and their effects on immune stimulation from US Patent 6,194,388 and US Patent 6,239,116 of the specification (see page 23 lines 13-20), which describe methods for synthesizing nucleic acids with modified backbones. Applicants argue, the state of the art was aware, not only of backbone modifications to influence the immunostimulatory capacity of a nucleic acid, but also of methods of synthesizing and optimizing nucleic acids containing backbone modifications.

Art Unit: 1645

C) Amount of direction provided by the inventor(s) and Quantity of experimentation needed to practice the invention: Applicants state the specification provides numerous specific examples of backbone modifications and describes identifying features of such modifications. Applicants state the art was familiar with how to make nucleic acids comprising a defined sequence, and having a naturally occurring or modified backbone. In addition, the specification teaches de novo synthesis and/or modification of nucleic acids using any number of procedures (see pages 16-23). Applicants state the examples section provides multiple examples of assays that can be used to test the immunostimulatory capacity of nucleic acids thus, sufficient guidance is provided in the specification to allow one of ordinary skill in the art to synthesize immunostimulatory nucleic acids that comprise SEQ ID NO: 1 and one or more backbone modifications. Applicants state that any optimization of such backbone modifications, or dosage requirements for nucleic acids containing such backbone modifications, would involve only routine experimentation. Applicants state that methods for generating backbone modifications and assays for testing the immunostimulatory capacity and relative activities of nucleic acids and also discloses methods for synthesizing nucleic acids and introducing backbone modifications, for example on pages 16-23 were routine in the art, as of the filing date of the instant application, and is demonstrated by the references cited and incorporated by reference in the instant application.

Examiner's Response to Applicant arguments:

In response to applicant's statement in (A) as set forth supra, although one of ordinary skill in the art would be familiar with synthesis and optimization of immunostimulatory nucleic acids including the incorporation of backbone modifications, as shown by the cited art is unpersuasive for the reasons set forth supra. To begin with, the independent claim is drawn to a composition comprising an immunostimulatory nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1, wherein the immunostimulatory nucleic acid has a nucleotide backbone which includes at least one backbone modification, however, the specification is only limited to the immunostimulatory nucleic acid comprising SEQ ID NO: 1 also known as in the art as ODN 10105 (see pgs. 12 and 87). Also the instant claims encompass an immunostimulatory nucleic acid that includes both those that are methylated and unmethylated. The specification does not provide adequate description of the claimed genus of nucleotide backbone modifications in an

Art Unit: 1645

immunostimulatory nucleic acid. Moreover, Applicant has not demonstrated which nucleotide backbone modifications in an immunostimulatory nucleic acid possess the abilities of the claimed immunostimulatory nucleic acid of SEQ ID NO: 1. Consequently, the number of species disclosed by the specification is not representative of the genus of nucleotide backbone modifications in an immunostimulatory nucleic acid encompassed by the claimed genus.

Applicant is reminded that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Therefore the written description rejection is maintained.

In response to applicant's statement in (B) as set forth supra, in regards to the reference Yu et al that reveals a predictable trend of dose-dependent immunostimulatory capacity of nucleic acids and based on this reference, one of ordinary skill in the art would have predicted that a backbone modification would not render inert an immunostimulatory nucleic acid is not relevant to the claims. Moreover, in regards to Applicants response, that the art discloses a sequence that contains the optimal 8 nucleotide motif on the 5' end and also contains an optimal 6 nucleotide motif was more immunostimulatory than a sequence containing a CpG motif that is optimal for activating mouse cells (GACGTT) and the art disclosed by Hartman et al is not relevant to the claims. For the reasons that Point 1: the claims are directed to a composition comprising an immunostimulatory nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1, wherein the immunostimulatory nucleic acid has a nucleotide backbone which includes at least one backbone modification; Point 2: as indicated by Yu et al, the art has not determined whether any immunostimulatory nucleic acid with any modified backbone is able to possess the abilities of the claimed immunostimulatory nucleic acid. Furthermore, Yu et al is cited to reveal the effects of oligonucleotides and structural changes that potentiate or suppress immunostimulatory activities of CpG oligos and also reveal oligonucleotides with no non-ionic linkage showed the ability to induce cell proliferation, however replacing a negatively charged phosphorothioate internucleoside linkage with a non-ionic methylphosphonate linkage resulted in the loss of lymphocyte proliferative activity which show that the state of the art is unpredictable to the claimed invention and therefore the claimed invention is not properly disclosed. In regards to the reference of Krieg et al. Antisense and Nucleic Acid Drug

Art Unit: 1645

Development (1996) 6:133-139 cited by Applicants to show that all of the immunostimulatory nucleic acids showed a dose-dependent immunostimulatory capacity (See Figs. 1-3) and the only sequences that exhibited no dose-dependent increase in immunostimulatory activity were the negative controls that lacked CpG dinucleotides does not indicate the genus and thus is unpersuasive. Moreover, the art teaches that all CpG nucleic acids are not alike and that different effects are observed with different CpG nucleic acids aforementioned above therefore the state of the art was not aware of any backbone modifications possess the abilities of being immunostimulatory in SEQ ID NO: 1 as claimed.

In response to applicant's statement in (C) as set forth supra, in regards to Applicants response that state the specification provides numerous specific examples of backbone modifications and describes identifying features of such modifications is unpersuasive. The specification is only limited to the immunostimulatory nucleic acid comprising SEQ ID NO: 1 also known as in the art as ODN 10105 (see pgs. 12 and 87). Also the instant claims encompass an immunostimulatory nucleic acid that includes both those that are methylated and unmethylated. The specification does not provide adequate description of the claimed genus of nucleotide backbone modifications in an immunostimulatory nucleic acid. Moreover, Applicant has not demonstrated which nucleotide backbone modifications in an immunostimulatory nucleic acid possess the abilities of the claimed immunostimulatory nucleic acid of SEQ ID NO: 1.

Consequently, the number of species disclosed by the specification is not representative of the genus of nucleotide backbone modifications in an immunostimulatory nucleic acid encompassed by the claimed genus. Applicant is reminded that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Therefore the Applicant's response to the examples aforementioned above and the methods for generating backbone modifications and assays for testing the immunostimulatory capacity and relative activities of nucleic acids as discussed above are not deemed persuasive.

As outlined previously, the specification is not enabled for a composition, wherein the immunostimulatory nucleic acid has a nucleotide backbone which includes at least one backbone

Art Unit: 1645

modification (claim 16), wherein the nucleotide backbone is chimeric (claim 18), wherein the nucleotide backbone is entirely modified (claim 19).

Furthermore, the specification does not reasonably enable any composition, wherein the immunostimulatory nucleic acid has a molecule nucleotide backbone which includes at least one backbone modification (claim 16), wherein the nucleotide backbone is chimeric (claim 18), wherein the nucleotide backbone is entirely modified (claim 19). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

(A) The nature of the invention;

(B) The breadth of the claims;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention: The instant claims are drawn to a composition, wherein the immunostimulatory nucleic acid has a molecule nucleotide backbone which includes at least one backbone modification (claim 16), wherein the nucleotide backbone is chimeric (claim 18), wherein the nucleotide backbone is entirely modified (claim 19).

Breadth of the claims: The claims encompass any composition comprising SEQ ID NO: 1, wherein the immunostimulatory nucleic acid has any type nucleotide backbone modification which includes at least one backbone modification (claim 16), wherein the backbone modification is a phosphorothioate modification (claim 17), wherein the nucleotide backbone is

Art Unit: 1645

chimeric (claim 18), wherein the nucleotide backbone is entirely modified (claim 19).

Consequently, the instant claims encompass a plethora of defined modification.

Guidance of the specification/The existence of working examples:

The specification discloses immunostimulatory nucleic acid comprising SEQ ID NO: 1 also known as in the art as ODN 10105 (see pgs. 12 and 87). The specification discloses nucleotide backbone modifications (see pg. 4 and 19). The specification discloses various chemical modifications and substitutions (see pg. 16 lines 1-5). The specification does not provide adequate description of the claimed genus of nucleotide backbone modifications in an immunostimulatory nucleic acid.

Applicant has not demonstrated which nucleotide backbone modifications in an immunostimulatory nucleic acid possess the abilities of the claimed immunostimulatory nucleic acid of SEQ ID NO: 1. However, the specification is only limited SEQ ID NO: 1. Therefore the data fails to show nucleotide backbone modifications in SEQ ID NO: 1. Therefore, one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model. The working examples do not disclose any empirical data or results indicative of a specific backbone modifications (pgs. 80-94).

State of the art: The art indicates Yu et al, whom study the effects of oligonucleotides and structural changes that potentiate or suppress immunostimulatory activities of CpG oligos. Yu et al teach oligonucleotides with no non-ionic linkage showed the ability to induce cell proliferation, however replacing a negatively charged phosphorothioate internucleoside linkage with a non-ionic methylphosphonate linkage resulted in the loss of lymphocyte proliferatory activity (see "Effect of non-ionic internucleoside methylphosphonate linkage in the 5'-flanking sequence" pg. 2804 column 2). Furthermore Yu et al teaches that the non-ionic phosphate linkages may enhance suppress, or maintain immunostimulatory activity compared with an unmodified CpG oligo, depending on the position of the substitution (see pg. 2806 column 1).

Therefore, the state of the art demonstrates that the effect of a given backbone modification on a given nucleic acid is unpredictable and can only be determined empirically.

In conclusion, the claimed invention is not enabled for any composition any composition comprising SEQ ID NO: 1, wherein the immunostimulatory nucleic acid has any type nucleotide backbone modification which includes at least one backbone modification. The specification

Art Unit: 1645

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention. The specification fails any working examples that disclose any empirical data or results indicative of specific backbone modifications (pgs. 80-94). The state of the art teaches that there are limitations the instant claim aforementioned above thus the state of the art are unpredictable. In view of the lack of support in the art and specification, it would require undue experimentation on the part of the skilled artisan to make and use as claimed; therefore the claims are not enabled. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed composition.

New Grounds of Objections

Claim Objections

7. Claim 17 is objected to for being dependent on a rejected base claim.

Conclusion

8. Claims 1-13, 20, 22, 27-32, 43, and 99 are allowed.
Claims 16 and 18-19 are rejected.
Claim 17 is objected as being dependent on a rejected base claim.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Art Unit: 1645

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert B Mondesi/
Supervisory Patent Examiner,
Art Unit 1645

Nina A Archie
Examiner
GAU 1645
REM 3B31